Specificity of the family of lysine methyltransferases SUV4-20H in prostate cancer

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Résumé

Despite significant advancements in the management of localized prostate cancer (PCa), this cancer remains a leading cause of mortality, primarily due to the limited efficacy of treatments against advanced and metastatic stages. Through an analysis of clinical data, we have identified the lysine methyltransferase SUV4-20H2 as a novel marker in patients with aggressive disease, exhibiting associations with specific PCa features. Our genetic investigations unveil the protumoral functions of SUV4-20H2 at gene regulation levels, which are counteracted by its paralog SUV4-20H1. However, concurrent targeting of both SUV4-20H enzymes presents a promising therapeutic approach for advanced prostate cancer independently of their role in gene regulation. Utilizing in vitro and xenografted models, we demonstrate that the pharmacological inhibition of SUV4-20Hs followed by the depletion of H4K20me2/3 marks synergistically enhances the efficacy of topoisomerase II (TOP2) poisons, notably etoposide, without inherent toxicity. Mechanistically, we show that this lethal synergy is linked to an enhancement of the etoposide-induced trapping of TOP2 complexes on chromatin upon SUV4-20H inhibition in proliferating prostate cancer cells. This might be related to specific alterations in heterochromatin structure and replication in absence of H4K20me2/3 states. Furthermore, the augmented trapping of TOP2 complexes upon loss of SUV4-20H is also associated with specific alterations in homologous recombination, resulting in extensive accumulation of double-strand DNA breaks at the end of S-phase and subsequent cancer cell death. Altogether, our findings establish SUV4-20H enzymes as pivotal players in cancer pathogenesis and promising targets for novel therapeutic intervention in combination with topoisomerase poisons that are currently used for cancer treatment.

Mots-Clés: Prostate cancer, SUV420H enzymes, H4K20 methylation, Topoisomerase II, therapeutic approach

*Intervenant